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(71) Applicant: ONCOLOGY INNOVATIONS, INC. [US/US]; 11224 Tradewinds Boulevard, Largo, FL 33773–4411 (US).

(72) Inventor: CARROLL, Robert, G.; 11224 Tradewinds Boulevard, Largo, FL 33773–4411 (US).

(74) Agents: STEIN, Barry, A. et al.; Bernstein, Cohen & Pokotilow, Ltd., 12th floor, Seven Penn Center, 1635 Market Street, Philadelphia, PA 19103–2212 (US).

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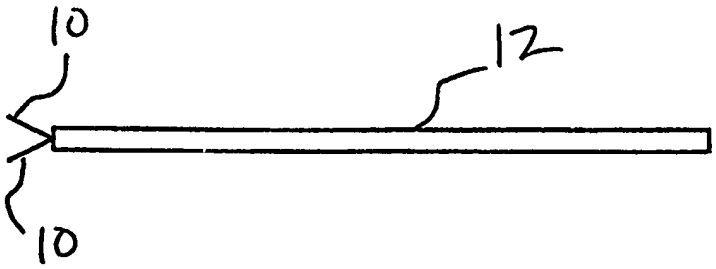
(54) Title: APPARATUS AND METHOD TO ENCAPSULATE, KILL AND REMOVE MALIGNANCIES

(57) Abstract

This invention is methods for conducting an operation on a living organism, including methods in which a channel is provided around a tissue of the organism, and an encapsulating tissue in a capsule. The capsule impedes material encapsulated therein from migrating to other tissues outside the capsule. An improved method of radiation therapy, in which a locally persistent radiation enhancing agent, such as iron dextran, is administered in or near a tissue to be treated, and a double hollow needle blade (10) with a trocar (12), is disclosed.



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APPARATUS AND METHOD TO ENCAPSULATE, KILL AND REMOVE MALIGNANCIES

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to the treatment of tumors within an organism, and more specifically, to encapsulating, destroying and removing malignant tumors from an organism.

BACKGROUND OF THE INVENTION

Death from cancer most often occurs from metastases which become apparent years after the attempted curative surgery. Tragically, the very acts of biopsy and surgical excision disseminate tumor cells into the systemic circulation and into the regional lymphatics. Improvement in long term cancer survival is dependent on answering two questions: (1) How can we accurately diagnose cancer without shedding tumor cells? (2) How can we surgically remove tumors without shedding tumor cells, and without stimulating any residual tumor cells?

New possibilities for concentrating rare circulating tumor cells from the peripheral blood and possibilities for detection of rare tumor cells in marrow may allow adequate certainty to proceed with lumpectomy as biopsy, avoiding one tumor shedding exposure. If clinical presentation and diagnostic images are shown to be more than 90 percent predictive in defined circumstances, biopsy may also be bypassed with adequate informed consent. In cases where biopsy cannot be eliminated, strategies for minimizing tumor shedding should be evaluated. Broadly, both physical and chemical methods are possible.

Physical methods include blockade of lymphatics using injection of substances around the full three dimensional perimeter of the tumor (peritumoral injection) in order to clog or constrict the lymphatics. Peritumoral injection of the patient's fresh whole blood which has been freshly hemolyzed by

addition of sterile water for injection is a physiologically attractive maneuver. Not only are the lymphatics obstructed by red cells, but tissue clotting mechanisms are activated and small veins may clot. Edema should further close off lymphatics and small veins. Local macrophage activation may result in destruction of some tumor cells.

Peritumoral blockade is probably not adequate by itself to eliminate tumor shedding in cases where the tumor itself is surgically entered, rather than only pierced by a biopsy needle. If we want to excise small tumors with minimal invasion, we need a truly robust way to contain and kill spilled tumor cells.

Primary and metastatic malignant tumors can be treated by a variety of methods, including surgical excision, chemotherapy and radiation therapy. A primary goal of all of these therapeutic methods is to remove and/or inactivate the tumor while causing as little collateral damage as possible to healthy tissues within the organism being treated.

Surgical excision of a tumor with a minimum of collateral damage to healthy tissues has been facilitated by advances in the arts of microsurgery, endoscopic surgery and real-time imaging. In particular, surgical techniques using surgical/imaging devices enable surgeons to precisely distinguish in real-time between tissues to be removed and tissues to be preserved intact within an organism. Unfortunately, it has been found that the very act of surgically excising a tumor from an organism, no matter how precise the surgical technique, can cause the tumor to metastasize, thus causing collateral damage to healthy tissues which may not become clinically apparent for months or years, but which will almost always progress to kill the patient.

Although advances in chemotherapy also promise to minimize collateral damage, researchers still seek a "magic bullet" which would effectively target only malignant tissues for destruction, without damaging healthy tissues.

In the meantime, it has been proposed to surround the tumor with a barrier which would protect surrounding healthy tissues from the damaging effects of locally injected chemotherapy. See, e.g., U.S. Patent No. 5,458,597.

U.S. Patent No. 5,458,597 deals with creation of a diffusion barrier of heat coagulated tissue proteins in order to restrict the outflow of locally injected chemotherapeutic agents from the thermally created tumor crater. Necrotic tissues and the coagulation capsule are left behind, where they are at substantial risk of becoming infected.

U.S. Patent No. 5,472,441 teaches providing a radio-frequency induced tissue coagulation barrier around a tumor to contain locally injected chemotherapy. Only metastatic cancers with no prospect for cure would be suitable for such a palliative nonsurgical approach where the additional risk of shedding tumor cells by piercing the tumor is irrelevant because of the short lifespan of patients with metastatic disease. Failure to remove the killed tissues as taught in this patent places the patient at risk for infection.

Collateral damage to normal tissues adjacent to cancerous tumors also limits the effectiveness of radiation therapy. Radiation sensitizers have been sought to selectively increase damage to malignant tissues while sparing healthy tissues. Unfortunately, these radiation sensitizers can themselves be toxic to healthy tissues when injected at levels high enough to achieve their radiation enhancing effect, and/or might not persist in the area of the tumor for a time sufficient to enhance the effect of radiation on the tumor.

Thus, there is a still unsatisfied need for tumor therapies that are effective in removing and/or inactivating the tumor without causing significant collateral damage to healthy tissues, and without causing microscopic shedding of tumor cells which create diagnosable metastases months or years later.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The instant invention addresses at least the foregoing deficiencies of the prior art by providing methods for conducting an operation on a living organism, said method comprising:

providing a channel around a tissue of said organism; and

infusing into said channel an encapsulating composition to encapsulate said tissue in a capsule,

wherein said capsule impedes materials encapsulated therein from migrating to other tissue outside said capsule.

Also provided are apparatuses for performing methods of the invention.

The invention also provides an improved method of radiation therapy comprising administering a radiation enhancing agent in or near a tissue to be treated. The radiation therapy method can conducted with or without encapsulation.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in conjunction with the following drawings, which are not drawn to scale and in which like reference numerals designate like elements and wherein:

Figs. 1A, 1B and 1C are sequential side views of a double hollow needle blade embodiment of the apparatus of the invention being deployed through a trocar;

Fig. 2 is a side view of a deployed single hollow needle blade embodiment of the apparatus of the invention;

Fig. 3 is a side view of an ultrasonic tissue destruction and removal probe of the invention;

Fig. 4 is a front view of the probe of Fig. 3; and

Fig. 5 is a front view of an alternative embodiment of a tissue destruction and removal probe of the invention.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a method and an apparatus for creating a capsule which contains tissue to be treated, destroyed and/or removed, e.g., a tumor with adequate margins. The invention also provides a method and an apparatus for

treating tissues with radiation-enhancing agents, particularly residual tissues remaining when total tumor removal is impossible.

Although much of the specification specifically pertains to the treatment of tumors, the invention is not limited thereto. The invention encompasses the isolation, treatment, destruction, and/or removal of other tissues as well.

In embodiments of the invention, a capsule surrounding a malignant or potentially malignant tumor can be provided, which prevents significant collateral damage by metastasis to tissues outside of the capsule, and optionally allows the tumor within the capsule to be treated more aggressively, yet safely, using minimal invasive surgical techniques, including ultrasonic tissue ablation, resectoscope, chemical digestion, and the like. Such aggressive treatment can include the provision of radiation enhancing agents to any unresectable tumor residue and/or to the tissues surrounding the capsule which are at risk of harboring viable tumor cells.

A preferred method of a tumor treating method of the invention comprises:

(a) impeding fluid communication between the tumor and healthy tissues by reducing tumor vasculature and impeding fluid communication in tumor area lymphatics and veinules by injection-infiltration of materials causing sludging, clogging, constriction, compression, and/or coagulation;

(b) forming a channel by severing all the clogged lymphatics and the compressed or coagulated venules and veins and arteries surrounding the tumor without cutting the tumor;

(c) filling the channel with an encapsulating composition;

(d) forming the capsule;

(e) evacuating the capsule;

(f) internally sterilizing the evacuated capsule; and

(g) removing the capsule from the patient.

The fresh tissues exposed by removal of the capsule can by examined for residual tumor cells. If residual tumor cells are

detected, a new, larger capsule is created, evacuated and removed, as above. If complete surgical tumor excision is impossible, residual tumor is treated by local infiltration of radiation sensitizers and/or therapeutic deposition of radiation sensitizers and other tumor killing agents in a timed release artificial capsule.

Impeding Fluid Communication

Where local anatomy allows, the blood flow into and out of the cancerous tumor is blocked in a minimally invasive manner. Under Doppler ultrasound image guidance, the arteries supplying the tumor and the veins draining the tumor area are selectively coagulated outside the boundaries of the tumor by radio-frequency diathermal heat, preferably with a coaxial bipolar needle electrode. Use of Doppler ultrasound aids identification of blood flow in feeding arteries and draining veins and documents cessation of blood flow with successful diathermy heat coagulation. With successful devascularization, including vessels deep to the cancer, only the peritumoral lymphatic flow and flow in small veins remains to be blocked by chemical and or physical agents and processes, as discussed immediately below.

Flow in tumor area lymphatics and veinules is further decreased by injection-infiltration of materials causing sludging, clogging, constriction, compression and coagulation.

Peritumoral blockage of lymphatic flow and flow in small veins may be achieved by injection of appropriate substances such as combinations of the patient's own whole blood, which has been freshly hemolyzed by addition of sterile water for injection, the patients own fresh plasma, vasoconstrictors, and substances which greatly increase local interstitial fluid viscosity prior to cutting and encapsulation. These measures can further reduce tumor cell shedding by sludging, clogging, constricting, compressing and coagulating peritumoral lymphatics and venules during the cutting process.

Red blood cells average 7 microns in diameter, which is relatively large for lymphatic channels. When sterile water for

injection is added to blood, the red cells burst (hemolysis), creating abundant debris of smaller sizes more suited for clogging lymphatic channels.

Peritumoral tissue preparation, prior to cutting and encapsulation, can be accomplished by injecting:

(1) the patient's own fresh whole blood which has been freshly hemolyzed by addition of sterile water for injection.

(2) ferric lactate, which provokes an intense tissue reaction creating a rigid fibrous mass at the injection site. See Anghileri, Calcif. Tissue Int. 51: 83-84, 1992.

(3) any sclerosing solution, such as are used to sclerose varicose veins, including adrenaline, norepinephrine, 95% ethyl alcohol, thrombin, ethanolamine oleate, ethanolamine oleate iopamidole, oleic acids, aethoxysclerol, polyethylene glycols, polydocanol, prolamine (Ethibloc), minocycline solution, doxycycline solution, tetracycline solution, erythromycin solution, silver nitrate, bleomycin, talc, quinacrine colloids, quinacrine solutions, quinacrine-ionic copper solution, phenol, phenol almond oil, sodium tetradecyl sulfate and OK432.

(4) tissue factor, fibrinogen or fibrin to induce clotting.

(5) collagen or gelatin to raise extracellular fluid viscosity.

(6) distilled water to induce edema, swelling tissues to pinch off venules and lymphatics.

(7) polyethylene glycol, including co-polymers and photo-initiating agent, to dramatically raise extracellular fluid viscosity and induce transient tissue solidification.

Mechanisms of action include pharmacologic vasoconstrictions, physical tamponade, chemical sclerosis, tissue dehydration, edema and thrombogenesis.

Forming a Channel

One or more cutting devices (e.g., blades, needle blades, lasers, wires, cords, torches, particle beams, etc.) which do not cut the tumor, sever all the clogged lymphatics and the compressed or coagulated venules and veins and arteries surrounding a tumor. The artificial capsule is created by providing (e.g., forming, cutting, ètc.) a channel between the tumor and the surrounding healthy tissue.

In a preferred embodiment, a channel can be provided between the tumor-bearing tissue and surrounding healthy tissue by inserting at least one, and preferably an array, of shape memory metallic hollow side cutting blades or needles into the periphery of a tumor under real-time ultrasound, MRI, isotopic, x-ray guidance or combinations thereof. Preferably, the array comprises a plurality of deployable hollow radio-frequency or microwave antenna or laser or ultrasound energy activated needle blade elements. The array is expanded using cutting radio-frequency or microwave or laser or ultrasound power and rotating 1 to 20 energy depositing elements to cut and define a common onion-shaped, spherical or cylindrical surface, thus isolating a core of tumor-bearing tissue from adjacent healthy tissues, hopefully without tumor at the margins. In a preferred embodiment, every other (i.e., alternating) radio-frequency peripheral hollow element can be active or ground, producing a circumferential rather than a radial radio-frequency energy field. This blade design eliminates the need to pierce the actual cancer until after capsule formation, minimizing the chance to dislodge cells. Figs. 1A, 1B, 1C and 2 show needle blades 10 which create such a channel when deployed and manipulated through a trocar 12. In order to minimize the amount of healthy tissue placed (e.g., trapped) within the capsule , it is preferable to use advanced imaging and/or marking means to precisely distinguish between malignant and healthy tissues when creating the channel surrounding the tumor.

The individual blades 10 may be of reshaped spring steel, and may also be fabricated using a metal with shape memory or a

bimetallic spring material, wherein shape alters as a function of temperature to cause bending in response to applied energy activation.

Multiple rotations of the blades 10 are performed during slow advancement of the device under diathermy, microwave, laser, ultrasound cutting power. Real-time imaging ultrasound inspection as the process is being performed allows appropriate enlargement of the cut volume of tissue to include any detectable irregularities of tumor shape appearing too near the cut margin. Real-time ultrasound imaging inspection as the process is being performed allows assessment of the completeness of isolation of tumor from surrounding tissues, allowing timely appropriate remedial actions, prior to installation of capsule forming materials.

Filling the Channel

The channel is filled with an encapsulating composition to form a capsule wall. In embodiments, the encapsulating composition is extruded into the channel through the hollow blades 10.

Unlike the barrier taught in U.S. Patent No. 5,458,597, the capsule of the invention does not consist primarily of rigid, brittle heat denatured local tissue components, but rather consists predominantly of injected materials which mix with the patient's own wound blood to form a tough, flexible capsule. The capsule is preferably created by chemical reactions between naturally-occurring components of the patient's own blood, such as plasminogen and fibrinogen, and components of a capsule-forming composition comprising substances (e.g., collagen) that combine with the patient's body chemistry to create a tough, flexible capsule. Alternatively, the capsule may be created with a capsule-forming composition comprising a barrier-forming or film-forming substance, which forms the capsule without chemically reacting with naturally-occurring molecules. In any event, the encapsulating composition preferably transforms from liquid to (a preferably elastic)

solid form after being injected into the channel. Ultraviolet chemical curing lights, such as are commonly used for curing dental materials, may be used to initiate photopolymerization of capsule forming materials which have been doped with suitable photoinitiator compounds.

Covalent cross-linking of non-toxic biocompatable polymers has been accomplished in living animals with continuous films of good mechanical strength. See, e.g., West et al., "Comparison of covalently and physically cross-linked polyethylene glycol-based hydrogels for the prevention of postoperative adhesions in a rat model." Biomaterials 16:1153-1156, 1995. West et al. describe using the photoinitiator 2,2-dimethoxy-2-phenyl acetophenone at 900 parts per million and photopolymerizing the polyethylene glycol inside the living animal by 20 second exposure to 365 nanometer ultraviolet light, at 10 milliwatts/cm^2, to produce a strong, resilient, covalently cross-linked, continuous barrier that was intact for over 4 days.

Additional important work on engineering the desired strength co-polymerization is disclosed in Suggs et al., "Preparation and characterization of poly(propylene fumarate-co-ethylene glycol) hydrogels." Journal of Biomaterials Science Polymer Edn. 9: 653-666, 1998.

The encapsulating composition is adapted to provide a capsule which prevents migration of tumor cells into regional lymphatics and into veins during surgical manipulation and during surgical removal of the abnormal tissue. Preferably, the encapsulating composition is adapted to provide a capsule which contains the chemical and physical tumor sterilization-destruction-digestion-fragmentation process, protecting adjacent tissues from chemical and physical damage attendant to tumor removal.

The encapsulating composition is preferably designed in view of the desired curing method. Curing (i.e., solidifying) can be a function of time, temperature and/or other naturally

prevailing or artificially provoked conditions. Thus, for example, the composition can comprise: components that react with each other to polymerize within a predictable amount of time after mixing; components that melt at a temperature above body temperature (i.e., > 37°C), are applied as a hot melt and cool to form a solid capsule at body temperature; components that react with naturally prevailing molecules in the patient to form solids or semi-solids; and/or components that polymerize in response to radiation (e.g., ultraviolet radiation applied after injection into the channel).

Suitable encapsulating compositions are formulated to provide capsules with properties that enhance or are complementary to the particular activities being performed within the capsule. Thus, for example, a biocompatible polymer that is resistant to the mechanical and/or chemical means for destroying the tumor is preferably selected. The encapsulating composition can comprise a combination of materials selected for their various advantageous properties. Materials potentially useful in artificial capsule formation can be found in the book *Surgical Adhesives and Sealants Current Technology and Applications*, edited by David Sierra et al. (Technomic Publishing 1996, Library of Congress #95-61620).

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The encapsulating composition is preferably physiologically compatible, although in certain circumstances physiological incompatibility is tolerable. For example, localized toxicity

is acceptable when the method is employed as a palliative measure in terminal patients.

It is particularly advantageous to include a marking agent (e.g., an imaging ultrasound, x-ray, magnetic resonance or combined marking agent) in the encapsulating composition so that the artificial capsule can be readily evaluated by imaging techniques, and if the capsule is to be removed at the end of the procedure, any remnants thereof remaining in the patient can be readily identified.

If the capsule is to be removed after its evacuation, it is advantageous to provide an elastic capsule which does not adhere to body tissues.

It should be noted that the capsule typically extends to and bonds with the perimeter of the introducing needle or trocar, forming a sealed system, sealed to the outer skin, open to the outside of the body. The length of the capsule to trocar seal may be increased by advancing the trocar further into the tumor while partly retracting blades 10 after the encapsulating composition has been freely applied within the channel.

The capsule provided by the methods and devices of the invention has at least the following beneficial effects. First, the capsule prevents materials inside the capsule from contacting and damaging tissues outside the capsule. Second, the capsule can enhance the anti-tumor effectiveness of the therapy by maintaining the focus of the therapy within a confined area surrounding the tumor.

Evacuating the Capsule

After the capsule has fully formed and optionally passed inspection of its integrity and scope (e.g., via real-time ultrasound, MRI, x-ray or fluoroscopy), any combination of chemical, physical and/or mechanical means of tissue destruction are employed to destroy the contents of the capsule. Prior to beginning tissue liquefaction or mechanical tissue removal, it is desirable to chemically kill and disrupt and partially digest

most tumor cells with: desiccants, such as absolute ethyl alcohol; cell bursting agents, such as distilled water; free-radical catalysts, such as iron and copper ions; free-radical chemical reaction initiators, such as hydrogen peroxide and hypochlorite bleach solution; and/or halogenators such as iodine tincture. Enzymes, such as colligenase, chondroitin sulfate, and DNAase, as well as proteolytic enzymes, such as trypsin, which are physiologically secreted by the pancreas, may be used to digest tissues. Papain and other common biochemical enzymes may also be used. Use of radio-frequency cutting and coagulation as well as adaptation of the common resectoscope normally used for transurethral resection of the prostate are also appropriate. Ultrasound, laser, microwave or radio-frequency energy can be deposited in the tissue to be destroyed using tumor penetrating probes or through skin or nearby tissues such as the vagina, bowel wall, oral cavity or other energy transmission site external to the capsule.

Ultrasound energy can be very effective in tumor destruction-digestion-fragmentation. Ultrasound has been used in cataract emulsification and in brain tumor debulking. Ultrasound energy induces local hyperthermia which is beneficial in tumor killing and lysis. Local hyperthermia significantly increases the rate of all chemical reactions.

Mechanical means for tissue removal analogous to those employed in prostate surgery, including resectoscope, electrovaporization, microwave needle ablation and thermotherapy, high intensity focused ultrasound, and various forms of laser ablation, are all applicable to minimal access tumor therapy of artificially encapsulated tumors. See also "Surgical and Minimally Invasive Therapies for BPH," 3(1) Harvard Men's Health Watch (August 1998), which describes many techniques for removing prostate tissue from within the natural capsule.

Physical means of destroying the tumor within the previously created protective capsule, such as high power

diathermy coagulation, diathermy dehydration and diathermy cutting, are readily available using the cutting needle array that created the capsule wall space. Additional physical processes, such as, e.g., focal heating and focal freezing, are also suitable.

The invention enables complete removal of large tumors from anywhere in an organism through a small, minimal access puncture, by liquefaction and removal of the contents of the artificial capsule. Liquefaction is preferably accomplished by physical means, such as comminuting the tissue with a moving (e.g., rotating, reciprocating, etc.) slicing means (e.g., a spinning cord or blade) to which the capsule walls are resistant, and/or chemical means. Most preferably, the contents of the artificial capsule are liquefied using ultrasonic energy, preferably having a wavelength of about 20 to about 40 kilohertz, transmitted through a titanium wand incorporating irrigation and suction functions. Use of radio-frequency cutting and coagulation as well as adaptation of the common resectoscope normally used for transurethral resection of the prostate is also appropriate.

As is well known, the overwhelming majority of each cell is made up of water, along with lipids, and proteins including collagen. Thus, liquefaction of tissues is an attractive option for tumor removal. To liquefy tissues, one must burst lipid cell membranes. Tumor tissues may be particularly sensitive to destruction by high power ultrasound, even in the absence of pretreatment with hypotonic solutions, because tumor cells generally exhibit higher intracellular pressures than are found in normal cells. Pretreatment with absolute ethyl alcohol sucks water out of cells and injures cell membranes. Sterile distilled water subsequently administered rushes into the dehydrated cells, bursting them.

Membrane destruction may be done with physical energy, such as 20 to 40 kilohertz frequency high energy ultrasound, or by chemical means, or preferably by a combination of chemical

pretreatment, metallic colloid treatment, augmented by subsequent 20 to 40 kilohertz frequency high energy ultrasound. High power 20 to 40 kilohertz ultrasound bursts cell membranes especially well if prior exposure to a hypotonic solution has caused cells to swell. Such high energy ultrasound also focally heats tissues, and vastly increases chemical and catalytic reactivity of metallic powders or colloids which may have been previously deposited in said tissues. Conventional 20 to 40 kilohertz frequency high power ultrasound titanium probes which have heretofore been used for fat reduction surgery can be adapted for tumor removal. This technique produces micromechanical effects, cavitation effects, and thermal effects, as documented in Zocchi, "Ultrasonic Liposculpting," Aesth. Plast. Surg. 16:287-298, 1992. Zocchi advocates infiltration of large volumes of a physiologic salt solution 50% diluted with distilled water to render the cells vulnerable to ultrasound energy induced cell bursting. Zocchi also uses the enzyme chondroitin sulfate. As shown in Figs. 3 and 4, improvements over Zocchi's design (which more closely resembles the alternative embodiment of the invention depicted in Fig. 5) include a central passage 14 for irrigant and a coaxial suction cannula 16 adjustably positioned around a multi-edge, preferably titanium, ultrasound energy transmitting probe. Further improvements over Zocchi include use of absolute ethyl alcohol, followed by distilled water, as well as free-radical reaction catalysts, such as iron and copper ions, free-radical chemical reaction initiators, such as hydrogen peroxide and hypochlorite bleach solution, and halogenators, such as iodine tincture. Powders and colloids of iron and copper may provide significant chemical catalytic free-radical mediated tissue destruction by chemical and physical increase in reactive surface as documented by Suslick et al., "On the origin of sonoluminescence and sonochemistry," Ultrasonics 28(5) 280-290, September 1990.

Alternatively, a rigid tube may be inserted which has rows of orifices along its circumference through which cords, wires

or blades are radially deployed into the adjacent tissue. Multiple rows of radial elements are deployed into the encapsulated tissues in this manner to transmit ultrasound, microwave, diathermy or other energy forms into the tissue. The degree of destructive energy can be modulated to achieve the desired degree of cell killing and/or liquefaction. Similarly, a multiplicity of fine wires may be deployed, which are hollow at their core, thereby allowing hypodermic injection of selected chemical or biochemical substances throughout the volume of the tumor to selectively increase the tissue destruction either by more efficient coupling with the energy field being deposited, or in order to propagate chemical reactions that are induced by the deposition of energy. Specifically, free-radical reactions can be supported by the presence in tissue of elemental iron or copper, especially of selected valences.

Alternatively, the tumor can be macerated within the artificial capsule with a grinder suction probe modeled on "rotorooters" used to remove atherosclerotic plaque, a side cutting tissue auger with attached suction probe. Mechanical tumor removal can also proceed by more conventional mechanical tumor removal by resectoscope, side-cutting or end-cutting minimally invasive surgical instruments such as the ABBY™ or BIOPSYS™ systems, vacuum assisted auger or "rotorooter" tissue extraction, or various means of mechanical tissue maceration. The capsule contents can also be removed by endoscopic or direct visually guided dissection.

Wires, cords and/or fibers can be introduced and rapidly rotated like a WEED WACKER™ gardening device. Such rotatable elements can effectively mince tissue, allowing the suction removal of tissues that have been destroyed. In order to minimize the transmigration of viable tumor cells into the bloodstream or into the lymphatics, encysting and appropriate biochemical treatment of the tumor prior to mechanical mincing may be valuable. In one embodiment, thin metallic blades are advanced to extend beyond the diameter of the trocar in order to

engage tissue. The needle shaft in its entirety, or just the portion of the needle shaft that has the blade elements projecting therefrom, is then rapidly rotated coaxially with the needle shaft. Thus, an approximately cylindrical volume of tissue is minced *in situ*. Application of irrigation solution and application of suction facilitates the removal of the debris, leaving only healthy tissues behind.

There are many ways in which tissues can be mechanically minced or destroyed by movement of elements designed to whip, shred, or mince tissues. In general, a roughly spherical volume of tissue destruction can be readily achieved. Similarly, roughly cylindrical volumes of tissue destruction seem readily achievable. Additionally, more specialized volumes and shapes can be achieved by modification or repositioning of the tissue destructive elements emanating from the placement needles.

Micromotors exist which can individually drive the tissue destructive elements so that the individual elements can rotate as well as be moved by the movement of the shaft of the needle. That is, the elements can be rotated about their own axis or whipped about similar to a WEED WACKER™ while at the same time the shaft of the needle upon which they are mounted is also rotating on its own axis. In such a way, more extensive tissue destruction is rapidly achieved. One advantage of mincing, liquefying and removing the cancerous tumor is to assure that complete tissue destruction has, in fact, occurred. If the tumor is simply destroyed in its location and allowed to remain, a palpable lump persists. If the tumor, having been killed, is then minced, liquefied and withdrawn from the body, it is possible that healing may occur without production of a palpable area of scar tissue. Thus, assurance that the tumor is not regrowing would be provided.

Physical means of tissue dehydration and dicing, such as heat and cutting created by diathermy, can be useful. In the preferred diathermy embodiment, every other alternating diathermy peripheral element is either active or ground,

producing a circumferential rather than a radial diathermy energy field. This design eliminates a need to pierce the actual cancer, minimizing the chance to dislodge cells. The diathermy coagulation power can preferably be applied using the same alternating active or ground elements. For this use, cutting power is applied to the antenna array as it is pulled back from the created capsule wall, to a position about 2/3 the capsule diameter. To maintain clearance from the capsule wall closest to the surface, the trocar may be pushed further forward under ultrasound control. Much higher coagulation diathermy power is then applied under real-time ultrasound visualization to heat, kill, and shrink the tumor bearing tissues within the capsule, without injury to the capsule wall or to tissues beyond the capsule wall.

Alternatively, after capsule formation, a bipolar diathermy system with a central needle serving as ground electrode plus 1 to 20 wire antennas radiating to surround the central ground can be inserted into the encapsulated tumor to define a spherical or cylindrical diathermy field. The configuration may resemble antennas deployed on space satellites.

Many physical, chemical, and mechanical processes can dramatically reduce solid volume while killing cells, allowing removal of large volumes of tissue through minimal access surgery. It will be apparent to those having skill in the art that this and other features of the invention make the invention particularly advantageous for treating breast, brain and lung tumors.

Internally Sterilizing the Evacuated Capsule

After removal of the capsule's contents, it is preferred to sterilize the remaining inside capsule wall and instrument track.

Chemical tumor sterilization and destruction-digestion-fragmentation means include: dehydration by absolute ethyl alcohol, optionally followed by povodine-iodine, and then by osmotic cell bursting using distilled water or other hypotonic

solutions; enzymatic degradation, including digestion by collaginase and/or pappain; acid and/or base degradation; applying sodium hypochlorite solutions, applying hypertonic salt solutions, applying local hyperthermia, and applying tincture of iodine. Final sterilization of the tumor bed and instrument track can be achieved by providing chemical sterilization agents within the capsule's interior. Suitable chemical sterilization agents include free-radical catalysts, such as iron and copper ions, initiators, such as hydrogen peroxide and hypochlorite bleach solution, halogenators, such as iodine tincture, desiccants, such as absolute ethyl alcohol, and cell bursting agents, such as distilled water causing osmotic rupture. Physical heat from diathermy or cell membrane bursting from high power ultrasound is useful for final sterilization of the capsule interior, capsule exterior, and instrument track.

Removing the Capsule

The sterilized capsule wall is safely removed by peeling with a suitable tool, by resectoscope (e.g., as commonly used in prostate surgery), by endoscopic or direct surgical dissection, or by side-cutting or end-cutting minimally invasive surgical instruments, such as the ABBY™ or BIOPSYS™ systems. Capsule wall removal technique can mimic opening a sardine can by peeling the capsule membrane onto a key like tool. Removal of the capsule wall eliminates a palpable residue that could mask local tumor recurrence. Final treatment of the cavity after removal of the capsule wall by installation of residual action locoregional tumor bed and lymphatic treatment agents can be performed.

If the capsule wall is to be left in place, suitable sustained-release materials can be incorporated into the created capsule wall. Suitable sustained-release materials include, e.g.: chemotherapeutic agents; sterilization agents; biological response modifying agents, such as histamine, cytokines, and anti-growth factor blockers; and radiation-enhancing agents, such as ferric lactate.

The capsule interior can be examined by standard optical or video endoscopic or laparoscopic or other minimal access surgical tools.

Exposed fresh tissues are examined for residual tumor cells. In order to document the tumor-free status of normal tissue margins, pathology touch preparations are obtained from the freshly exposed tissue walls after the capsule has been removed from the patient. If margins are tumor positive, the procedure is repeated to encapsulate a larger volume of tissue, or a side lobe of tissue. In embodiments, an enlarged capsule is formed around a temporary support structure provided by a balloon expanded within the void created by evacuation of the contents of the original capsule.

If complete surgical tumor excision is impossible, residual tumor is treated by local infiltration of radiation sensitizers and/or therapeutic deposition of radiation sensitizers and other tumor killing agents in a timed release artificial capsule. In those cases in which residual tumor cells are adjacent to vital structures or tumor cell spread to adjacent tissue is likely, persistent chemical agents can be provided by direct injection and by incorporation in a specially formed therapeutic capsule wall for timed release to potentiate chemotherapy and radiation therapies. Radiation sensitization by metal catalyzed free-radical reactions can increase cancer cell destruction. Iron and copper compounds and colloids can be infiltrated into at-risk tissues by multiple closely spaced injections, or introduced into the retained capsule wall in order to potentiate other therapies such as systemic chemotherapy, non-ionizing radiation, ionizing radiation, and ultrasound energy deposition. The potential utilization of iron and copper salts as radiation sensitizers is novel. Radiation sensitizers include atoms having atomic numbers higher than the atoms in tissue, favoring greater interaction with the x-ray beam. A 30% increase in tumor radiation sensitivity allows much higher cancer cure rates with much lower damage to normal tissues. Moreover, iron and

copper are intrinsically highly catalytic for free-radical reactions, especially when ionized by incident x-rays. These metals may also be activated by ultrasound energy, and potentially by laser energy.

When the formulations are being used for post-operative therapy or for treatment outside of the capsule, they are preferably locally persisting, so as to concentrate their effects where most needed. For example, iodine compounds used for conventional x-ray contrast can be reformulated as colloids or small particles which can remain in the tissues long enough to facilitate-radiation therapy treatments lasting many weeks.

Tumor killing effectiveness of each unit of absorbed radiation can be greatly enhanced by maximizing formation and propagation of the free-radical reactions initiated when ionizing radiation knocks electrons off target molecules. Iron and copper are potent catalysts for free-radical reactions within the living body. Iron and copper also have atomic numbers greater than tissue, increasing the likelihood of interaction with the radiation therapy beam. The invention also encompasses the prophylaxis and treatment of local and regional lymphatic vessels and nodes with extended release forms of biological response modifiers, iron and copper compounds, and extended release forms of conventional cancer chemotherapeutics, infiltrated into tissues surrounding the removed capsule wall or slowly released from biodegradable resorbable capsule wall. Physical ultrasound interaction of metallic powders and colloids produces surface chemical activation of intrinsically catalytic compounds serving to greatly amplify the direct physical tissue destruction effects of ultrasound energy. The artificial capsule can be formulated to include a wide range of physical, chemical and/or biological therapeutic agents which are slowly released (i.e., sustained-release agents) to provide local tissue treatment and locoregional lymphatic treatment.

Collateral damage to normal tissues adjacent to cancerous tumors also limits the effectiveness of radiation therapy.

Radiation sensitizers have been sought to selectively increase damage to malignant tissues while sparing healthy tissues. Unfortunately, these radiation sensitizers can themselves be toxic to healthy tissues when injected at levels high enough to achieve their radiation enhancing effect, and/or might not persist in the area of the tumor for a time sufficient to enhance the effect of radiation on the tumor.

It is generally recognized that transition metals, including Cu^{+}, Fe^{2+}, Sn^{3+}, Co^{2+} and Ni^{2+}, have all been demonstrated to be a source of catalysis of free-radical reactions in biological systems. Thus, the tumor sterilization and destruction-digestion-fragmentation can be achieved by oxidation by iron or copper catalyzed free-radical chemical reactions, including sodium hypochlorite bleach or hydrogen peroxide free-radical reaction initiating and sustaining compounds. Cu^{2+} associates with the guanine-cytosine base pair of DNA to create local free-radical damage to the DNA characteristic of attack by hydroxyl ion. Copper is a powerful promoter of free-radical damage to lipids, proteins, and especially to DNA and its bases. See Aruoma, "Copper ion-dependent damage to the bases in DNA in the presence of hydrogen peroxide," Biochemical Journal 1991, 273: 601-4.

Neither copper nor iron ions can exist free in aqueous solutions at pH 7.4, partly because body fluids contain phosphate and bicarbonate ions and any available metal ions must bind to biologic molecules. Damage caused when metal ions react with hydrogen peroxide to form hydroxyl radical will thus be directed to the site of metal ion binding.

The biologic implications of site specificity of hydroxyl ion formation are profound. $Fe^{2+/3+}$ reacts with super oxide anion, $\bullet O_2^-$ and hydrogen peroxide via the Haber-Weiss mechanism to generate extremely reactive hydroxyl radicals.

Iron-catalyzed injury results in damage to cell constituents, including oxidative damage to lipid membranes, proteins, nucleic acids, mitochondria, lysosomes, and the

sarcolemmal membrane. Many pathological events are thought to be associated with peroxidation of lipids in biological membranes. This peroxidation proceeds by a free-radical chain reaction (1 - 3):

(1) LH -----> L•

(2) L• + O_2 -----> LOO•

(3) LOO• + LH -----> LOOH + L•

wherein LOO• is the lipid peroxy radical.

The initiation reaction (1) is one of the key steps. Iron is a well-known catalyst of initiation step (1), and iron-oxygen species have been suggested to be responsible for initiation of peroxidation. However, it has been pointed out that since biochemical membrane systems always contain traces of preformed lipid peroxide (LOOH), added iron is more likely to stimulate peroxidation by decomposing lipid peroxide to the alkoxy radical (LO•) (4) than by generating initiating species.

(4) LOOH + Fe^{2+} -----> LO• + Fe^{3+} + OH^-

(5) LO• + LH -----> LOH + L•

LOOH-dependent lipid peroxidation plays an important part in oxidative deterioration of biological membranes.

Goldstein et al., in "Transition metal ions and oxygen radicals," Int. Rev. Exp. Pathol. 31: 133-64, 1990, proposed a "site-specific" Fenton mechanism in which the binding of a transition metal ion to the biological target is a prerequisite for the production of OH radical-mediated cell damage.

Schaich et al., in Lipids 23: 570-79, 1988, proposed that the solubility of iron complexes in the lipid phase of membranes is a critical determinant of their catalytic effectiveness in initiating lipid peroxidation. Iron ions likely arrest cell growth by chemically generating hydroxyl radicals from lipid peroxides.

Treatment of locoregional lymphatics may be performed by inclusion of therapeutic colloids and slow release chemical formulations within the materials forming the capsule wall and/or by direct injection of therapeutic materials outside the

capsule wall. Such therapeutic substances may include conventional antineoplastic agents, including colloidal forms of such agents designed for sustained-release and preferential lymph node targeting. Suitable therapeutic substances include colloidal radioactive agents, hormonal agents, biological growth modifiers, growth factor blocking agents, DNA transacting viral probes, and free-radical catalytic chemical means.

Iron dextran is a U.S. Food and Drug Administration approved injectable agent formulated for intravenous or intramuscular injection. A suitable dose is about 100 milligrams of iron in 1 milliliter of volume.

The possibility of using iron compounds as radiation sensitizers was disclosed in abstract form by Nelson et al. in 24 Cell Proliferation 411 (1991):

> Although 32 micrograms/ml ferritin was not toxic, it reduced clonogenic-cell survival after x-irradiation by approximately 75%, from about 0.66 to 0.17 at 4.0 Gray. But, at doses above 48 micrograms/ml, toxicity increased appreciably in a dose dependent manner.

This work subsequently appeared as a full paper entitled "Ferritin-iron increases killing of Chinese hamster ovary cells by x-irradiation" in Cell Proliferation 1992 25:579-585.

This work has attracted little notice and has never been tried as therapy in human beings. A significant problem with the use of iron as a radiation sensitizer involves the property of stimulating tumor growth at sub-toxic iron concentrations as documented by Stevens et al. in Iron, Radiation, and Cancer. Environmental Health Perspectives 87:291-300, 1990. Thus, the prior art teaches that growth of metastases outside the radiation field will be stimulated at the same time that cell killing inside the primary tumor is increased, yielding an unacceptable tradeoff.

The current invention overcomes this difficulty by teaching the local administration of persistent timed release (i.e., sustained release) forms of iron such as iron dextran supplied as 100 milligrams/ml in the vicinity of the tumor in conjunction with systemic administration of iron chelating agents. Concentrations of iron that are directly tissue toxic, far in excess of 48 micrograms/ml, are released locally from the iron dextran. By the combination of direct tissue iron toxicity, and local radiation sensitization within the diffusion zone surrounding the persistent iron dextran, significantly increased tumor control can be achieved. Addition of systemically administered iron chelating agents by periodic intravenous administration provides protection against the metastasis growth promoting effects of elevated systemic iron levels.

There are several tumors which kill primarily by local invasion, such as brain glioblastoma multiforme and pancreatic cancer, and in which the role of metastatic disease is minimal. Such carefully selected tumors may benefit from local tissue iron toxicity and local radiation sensitization, without the necessity of systemically administered iron chelating agents. Tumors with any metastatic potential are best treated with systemically administered iron chelating agents.

If the radiation enhancing material is, for example, injected directly into the prostate gland through the rectal wall, the prostate would be diffusely labeled and some iron dextran would flow out into lymphatics draining the prostate. Thus, the intra prostate cancer area as well as the lymphatics that may harbor spread of prostate cancer can both receive the benefits of enhanced radiation therapy effectiveness when those areas are treated.

Similarly, if iron dextran or other persisting iron/copper compounds are directly injected into lung cancers or other solid tumors through CT, MR or ultrasound guided needles in a technique resembling needle biopsy, the benefits of this

radiation sensitization technique could extend to all solid tumors.

Iron dextran or other persisting iron/copper compounds can also be deposited into tumors through bronchoscopic methods, or by angiographic injection into feeding arteries. Injection into the portal veins of the liver may be useful for some tumors. Direct lymphatic injections may also be useful.

Ferricenium salts can act as radiosensitizers of hypoxic cells. The toxicity of these metal complexes, but not their radio-sensitizing ability, is reduced by including serum albumin in the medium. See, e.g., Joy et al., in J. Radiation Oncology Biol. Phys., 16: 1053-56, 1989 and Teicher, et al., in Radiation Research 109: 36-46, 1987.

U.S. Patent 5,246,726 discloses oral administration of an essential fatty acid along with oral administration of iron. It does not mention the possibility of intravenous preparations of fatty acids in which appropriate daily doses are given by intravenous administration of fatty acid emulsions coupled with daily doses of iron given either in the same preparation or by another route, for example, iron dextran or iron sorbitol preparations for intramuscular injection in the treatment of persons suffering from cancer. The patent discloses that the cancer cell killing effect of fatty acids is dramatically enhanced when the fatty acids are provided to cancer cells in the presence of iron within a culture. There is no use of ionizing radiation in the patent.

Lesnefsky, "Tissue Iron Overload and Mechanisms of Iron-Catalyzed Oxidative Injury," in *Free Radicals in Diagnostic Medicine*, pp. 129-146 (Plenum Press, N.Y. 1994), points out that the heart is the most susceptible organ to damage in iron overload states, sustaining injury at approximately one thousand micrograms of iron per gram of tissue. Iron is essentially insoluble in physiological buffers. As the recommended usual dose of iron dextran is 100 milligrams of iron in 1 milliliter of volume, there is a significant therapeutic to toxic ratio of

10 to 1, sparing uninvolved tissues and yet sensitizing tumors and draining lymph nodes to radiation therapy.

Iron bound to negatively charged ligands including citrate, ammonium citrate, nitrofluoracetic acid, or adenosine diphosphate has increased solubility which enhances the redox-cycling of iron, allowing iron to catalyze oxidative damage. Redox-cycling by iron between Fe^{2+} and Fe^{3+} damages biomolecules. $Fe^{2+/3+}$ reacts with super oxide anion and hydrogen peroxide via the Haber-Weiss mechanism to generate extremely reactive hydroxyl radicals.

Super oxide anion or ischemia can radioactively release iron from ferritin into the redox-active cytosolic pool. Iron is present in ferritin as Fe^{3+}, and reduction to Fe^{2+}, either by O_2-ascorbate, or other mechanisms, results in the release of iron into pools that can catalyze oxidative injury. Similarly, during oxidative stress, hydrogen peroxide can release iron from hemeproteins, exacerbating oxidative damage. Ischemia causes approximately a 10-20 nM increase in cytosolic iron.

Acidic environments caused by ischemia or inflammation can result in the release of iron from Tf, even at physiologic levels of iron saturation.

Redox-cycling by iron between Fe^{2+} and Fe^{3+} damages biomolecules, causing cell injury. $Fe^{2+/3+}$ reacts with super oxide anion and hydrogen peroxide via the Haber-Weiss mechanism to generate the very reactive hydroxyl radical. The second reaction between Fe^{2+} and hydrogen peroxide that generates $\bullet OH$ is the Fenton reaction.

The generation of "free" hydroxyl radical may not actually occur. Instead, a highly-reactive "crypto" hydroxyl radical in the iron coordination complex, perhaps the perferryl ion, may be the oxidizing species. Iron-catalyzed hydroxyl radical formation requires at least one aqueous coordination site in the iron coordination sphere.

Iron ligands such as EDTA, sugars, citrate, and nucleotides (including ATP and ADP) allow water in the iron coordination complex and catalyze subsequent iron-catalyzed •OH formation.

Haber-Weiss Reactions:

$Fe^{3+} + \bullet O_2^- \text{ ----> } Fe^{2+} + H_2O_2$

Fenton reaction:

$Fe^{2+} + H_2O_2 \text{ ----> } Fe^{3+} + \bullet OH + OH^-$

In the cell, •OH causes oxidative damage to DNA, membrane lipids, and proteins. Protein damage can involve protein sulfhydryl oxidation, carbonyl group formation, or oxidative bond cleavage. Protein damage leads to enzyme inactivation, structural protein alteration, and often accelerated proteolysis. Oxidative DNA damage causes strand breaks and cross-linking, as well as the hydroxylation of bases, the latter providing a marker of oxidative damage to DNA. By any of these mechanisms, oxidative damage to DNA increases the incidence of mutations. Iron can both initiate and propagate lipid peroxidation, leading to altered membrane fluidity, inactivation of membrane-bound enzyme complexes, and eventual membrane disruption.

Fe^{2+} bound to ADP and ATP is an especially good catalyst for •OH generation, and of potential physiologic importance as well. The Fenton reaction between Fe^{2+}, -ADP and hydrogen peroxide clearly damages tissues.

While the Haber-Weiss and Fenton reactions have been widely considered as potential causes of iron-catalyzed lipid peroxidation, the ability of iron to cause oxidative damage by redox-cycling independent of oxygen metabolites has also been described. Fe^{2+} -ADP chelates alone cause oxidative damage to myocardial lipids, and the lag phase prior to the initiation of oxidative damage is reduced by the presence of small amounts of Fe^{3+}. $Fe^{3+/2+}$ ratios of 1:1 to 7:1 result in the highest rates of lipid peroxidation.

Complexes of iron with molecular oxygen may be the active species. The potential for similar direct non-oxyradical

mediated iron-redox cycling to damage proteins or DNA has not been adequately explored.

Fe^{2+} -ADP is an efficient initiator, but does not result in propagation. However, Fe^{2+} -EDTA is an efficient propagator of lipid peroxidation. Thus, iron could be involved in damage to cell membrane lipids in at least three ways: (1) iron-generated •OH could initiate lipid peroxidation (2) iron could initiate lipid peroxidation independent of •OH; or (3) iron could propagate lipid-radical chain reactions via lipid peroxide decompositions independent of •OH.

Exposure of rat liver mitochondria in vitro to 1-3 mM Fe^{2+}-chelates increases lipid peroxidation and progressively inhibits electron transport. The probable mechanism involves iron catalyzed oxidative damage to mitochondrial membrane lipids, with alteration of the inner membrane environment, and subsequent inhibition of the membrane associated enzymes of the electron transport chain.

Even prior to the onset of electron transport defects, subtle iron overload increases mitochondrial lipid peroxidation and calcium release. Mitochondrial calcium release initiates subtle cycles of calcium uptake and release from mitochondria that consume energy and impair cellular calcium homeostasis, predisposing to cell damage.

The primary importance of intracellular iron stores is as the catalytic site of oxidative damage during reperfusion. The $•O^{2-}$ and hydrogen peroxide precursors of iron-catalyzed injury can be generated either internal or external to the cell, yet still participate in intracellular iron-catalyzed oxidative damage.

Hydrogen peroxide can diffuse across cell membranes, while super oxide can traverse anion channels. This finding is consistent with results in cell culture that target cells provide the intracellular iron for their own destruction, even when $•O^{2-}$ and hydrogen peroxide are generated in the extra cellular space.

Increased redox-active iron present in hemeproteins and the cytosolic iron pool can catalyze oxidative damage to lipids, proteins, and nucleic acids, either by oxyradical dependent or independent mechanisms.

Iron-catalyzed injury results in damage to cell constituents, including mitochondria, lysosomes, and the sarcolemmal membrane. These mechanisms of iron-mediated damage are involved in the pathogenesis or organ dysfunction in primary hemochromatosis, transfusion-related iron overload, ischemia-reperfusion injury and cardiac anthracycline toxicity.

DNA, cellular proteins, lipid membranes, mitochondria and other cellular organelles are targets for molecular damage caused by either covalent binding of primarily electrophilic, but in some cases free-radical, reactive intermediaries and direct free-radical initiated oxidative stress resulting in target oxidation.

Castilho et al., in Archives of Biochemistry and Biophysics, Vol. 308, No. 1, January, pp. 158-163, 1994, have reported on oxidative damage of mitochondria induced by Fe(II)citrate is potentiated by Ca^{2+} and includes lipid peroxidation and alterations in membrane proteins. Both oxygen radical formation and Ca^{2+} seem to be involved in the overall process of cell injury associated with oxidative stress. The mitochondria is an important cellular site of both generation of oxygen radicals and oxidative damage. It is well known that iron complexes induce extensive lipid peroxidation and irreversible damage in isolated mitochondria. Iron citrate can shift the $Fe^{3+/2+}$ couple reduction potential from +0.77V to +0.33V, which causes a high rate of Fe^{2+} auto-oxidation. Castilho et al. conclude that Ca^{2+} potentiates the oxidative damage of mitochondria caused by Fe^{2+} citrate.

Fujii et al. recently reported on site-specific mechanisms of initiation by chelated iron and inhibition by alpha-tocopherol of lipid peroxide dependent lipid peroxidation in

charged micelles. See Archives of Biochemistry and Biophysics 284: 120-126. 1991.

In addition to the pathological events discussed above, which are thought to be associated with peroxidation of lipids in biological membranes, added iron reacts with the OOH-group of LOOH at the membrane surface to form LO•, and the LO• then penetrates into membranes and reacts with the unsaturated bonds of LA to initiate the chain reaction in a deep inner phase, where LOO• is generated.

Gutteridge has reported on "Ferrous-salt-promoted damage to deoxyribose and benzoate" in Biochem. Journal (1987) 243: 709-714.

Quinlan et al., in the paper, "Action of lead(II) and aluminum(III) ions on iron-stimulated lipid peroxidation in liposomes, erythrocytes and rat liver microsomal fractions," Biochemica et Biophysica Acta, 962: 196-200, (1988), found that aluminum Al^{3+} ions increase Fe^{2+} dependent liposomal peroxidation at pH 7.4 and at pH 5.5. Thus, this powerful effect is found over a concentration of 10 mM to 400 mM, and over acidic to alkaline pH values. The Fe^{2+} is largely acting by decomposing traces of preformed lipid peroxides in the membrane fractions to give chain propagating peroxyl and alkoxyl radicals.

Al^{3+} ions in aqueous solution undergo extensive hydrolysis at pH 7.4. Quinlan et al. hypothesize that Al^{3+} binds to the membrane surface, thus causing a localized freezing of phospholipid movement, facilitating the propagation of peroxidation. This work suggests that aluminum sulfate in concentrations of 10 mM to 400 mM in conjunction with ferrous ammonium sulfate at 100 mM produces catalytic effects. Phagocytic cells, such as monocytes and macrophages, may become activated by contact with foreign compounds and foreign particles in the treated tissue. Activated phagocytic cells produce toxic metabolites of oxygen coupled with the release of granular enzymes and the formation of highly reactive

metabolites such as hypochlorite. The entire range of white cells, including polymorphonuclear leukocytes, T-cells, basophils, eosinophiles, monocytes and macrophages, can be involved in tissue injury reactions. Such reactions may serve to initiate further propagation of oxidative free-radical injury.

Hydroxyl radicals are produced in living organisms by at least two mechanisms: (1) reaction of transition metal ions with hydrogen peroxide, and (2) homolytic fission of water caused by ionizing radiation. Hydroxyl radicals are extraordinarily reactive and attack all biologic molecules, usually setting off free-radical chain reactions. Transition metals, including Sn^{3+}, Cu^{+}, Fe^{2+}, Co^{2+} and Ni^{2+}, have all been demonstrated to be a source of catalysis of free-radical reactions in biological systems. Cu^{2+} associates with the guanine-cytosine base pair of DNA to create local free-radical damage to the DNA characteristic of attack by hydroxyl ion.

Different ligands to Fe^{2+} may stabilize this intermediate so that little hydroxide ion is formed, whereas others destabilize it. Iron ethylenediaminetetraacetic acid chelates are good sources of hydroxyl ion in the presence of hydrogen peroxide. Interestingly, the relatively slowly reactive Fe^{3+}, when interacting with ascorbate (Vitamin C), yields very highly reactive Fe^{2+} and semi-dehydroascorbate. Thus, iron salt-ascorbate and hydrogen peroxide produces abundant radicals. Aruoma et al., in the Journal of Biochemistry 264: 20509-12, 1989, documented "Damage to the bases in DNA induced by hydrogen peroxide and ferric iron chelates." They documented that ferric nitrilo tri-acetic acid produced the most DNA damage in the presence of hydrogen peroxide. Nitrilo tri-acetic acid was previously a common constituent of detergents and is now widely distributed in the environment.

Organisms take great care in the handling of iron, using both transferring transport protein and ferritin and hemosiderin storage proteins to minimize the amount of "free" iron within

cells and in extra-cellular fluids. This sequestration of transition metals is a very important contribution to antioxidant defenses. However, oxidative stress itself can provide iron for free-radical reactions. $\bullet O_2^-$ can mobilize iron from ferritin, and hydrogen peroxide can degrade. Copper is a powerful promoter of free-radical damage to lipids, proteins, and especially to DNA and its bases. See Aruoma "Copper ion-dependent damage to the bases in DNA in the presence of hydrogen peroxide." Biochemical Journal 1991, 273: 601-604.

The concentration of iron or copper ions catalytic for free-radical reactions within the body is extremely low because metal ion sequestration is highly effective. Neither copper nor iron ions can exist free in aqueous solutions at pH 7.4, partly because body fluids contain phosphate and bicarbonate ions. Any available metal ions must bind to biologic molecules. Damage caused when they react with hydrogen peroxide to form hydroxyl radical will thus be directed to the site of metal ion binding. The biologic implications of site specificity of hydroxyl ion formation are profound. The type of biologic damage produced by site specific free hydroxyl radical generation will not resemble that produced by attack of free hydroxyl ions generated by ionizing radiation. This has been documented in Von Sonntag, "The chemical basis of radiation biology" 1987.

Once tissue injury has been initiated by a free-radical cascade, additional injury mediators, such as prostaglandins, leukotrienes, interleukins, interferons, and tumor necrosis factors, may all play additional roles. White cells, especially phagocytes, also play an important role in furthering tissue injury. If bleeding is induced by injury to the walls of blood vessels in the tumor area, free hemoglobin is exposed to excess hydrogen peroxide producing heme degradation with further release of catalytic iron ions. Free heme is also a toxic agent.

Thus, an object of this invention in addition to providing artificial capsules for treating tumors is to selectively

increase tissue destruction either by more efficient coupling with the energy field being deposited or in order to propagate chemical reactions that are induced by the deposition of ionizing radiation. Specifically, free-radical reactions can be propagated by the presence in tissue of elemental iron or copper, especially of selected valences. Iron or copper ions and/or colloids can serve to profoundly alter the electromagnetic characteristics of tissue, thereby allowing more effective coupling of the ionizing radiation energy with the volume of tissue containing such increased concentrations of selected high atomic number catalytic materials.

A particularly preferred method of the invention comprises:

A. Preoperative, intraoperative and postoperative infusion of biological agents and pharmaceuticals to kill free floating cancer cells and to block implantation of shed tumor cells and to neutralize growth factors created by the surgical wound.

B. Monitoring the appearance of tumor cells in the peripheral blood during the entire biopsy and the entire surgical procedure.

C. Bipolar needle coagulation under Doppler ultrasound guidance to block arteries and veins surrounding the tumor from all sides and underneath.

D. Clogging lymphatics and compressing lymphatics and venules with adequate volumes of locally infiltrated fresh whole blood, and constricting peritumoral vessels with vasoconstrictors such as 1:800,000 epinephrine.

E. Cutting a complete channel around the entire tumor including at least a 1 cm margin of apparently normal tissue.

F. Filling the channel with the patient's fresh plasma, possibly with added collagen and the patient's concentrated fibrinogen.

G. Inspecting the capsule thus formed by imaging ultrasound, and thickening any apparently thin areas.

H. Injecting absolute ethyl alcohol to kill and dehydrate cells within the created capsule, followed by povodine-iodine to further sterilize the contents.

I. Mechanically fragmenting the tumor by means such as high power ultrasound with aspiration and/or resectoscope.

J. Chemically digesting the remaining cellular debris and flushing-out with suitable sterilizing solutions such as absolute ethyl alcohol and povodine-iodine and absolute ethyl alcohol solutions of iodine. These solutions may be heated to further speed cell killing.

K. Visually inspecting the interior of the capsule with an endoscope.

L. Incising and peeling away the artificial capsule wall.

M. Cauterizing bleeders under endoscope control or inflating a foley catheter balloon within the wound to stop bleeding.

N. Irrigating wound with physiological saline solution.

O. Obtaining touch preparations from the entire internal surface of the surgical site.

P. If touch preparations are negative, internal resorbable purse string sutures can be provided to obliterate the cavity. A solution of povidone-iodine diluted 1:10 with isotonic saline can be applied to potentially diminish local recurrence. Timed-release minocycline can be applied to oppose growth factors.

Q. If touch preparations are positive, the following options are appropriate:

a. Re-excision of a larger volume, possibly after purse string sutures to obliterate the cavity.

b. Local infiltration of persistent radiation sensitizers such as colloids of iron and copper.

c. Deposition of a therapeutic capsule wall providing long term timed release of radiation sensitizers, such as colloids of iron and copper.

Obviously, there is a need to minimize scarring at the area of tissue destruction. One way in which this may be achieved is by preventing significant hemorrhage into the cavity. Prevention of hemorrhage into the cavity may be achieved by installation of certain substances, such as fibrin, in order to limit the total volume of bleeding by rapidly initiating coagulation with minimal amounts of blood. Similarly, irrigation with suction through the needle until such time as no free blood is recovered through the needle lumen can serve to avoid having a post-operative clot form. In general, the smaller the amount of retained blood at the site of operation, the less the subsequent tissue lump formation, and the lower the release of platelet derived growth factor. Imaging through the trocar can be the final step in the sequence assuring that a clean wound is left behind.

It is possible to staple, sew and/or chemically bond the cavity walls together, if this is desired, through the same access wound using technologies similar to those found in laparoscopic surgery. In general, the current field of laparoscopic surgery relies upon human vision through a video link. The emerging field of needle/catheter ablation relies predominantly on indirect vision using displays that create images by modalities which are not native to human sensing, such as magnetic resonance, ultrasound, x-ray, nuclear, electrical impedance and imaging by infrared and other non-visible wavelengths of the electromagnetic spectrum.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

1. A method for conducting an operation on a living organism, said method comprising:

providing a channel around a tissue of said organism; and

infusing into said channel an encapsulating composition to encapsulate said tissue in a capsule,

wherein said capsule impedes materials encapsulated therein from migrating outside said capsule.

2. The method of claim 1, wherein said channel is provided by rotating at least one arcuate cutting device around said tissue.

3. The method of claim 2, wherein said at least one arcuate cutting device: (a) comprises a material having shape memory, (b) is deployed through a trocar in a linear state, and (c) assumes its arcuate state after passing through said trocar.

4. The method of claim 3, wherein radiant energy is applied to said at least one arcuate cutting device to alter its state from linear to arcuate.

5. The method of claim 4, wherein more than one said arcuate cutting device is rotated to provide said channel.

6. The method of claim 5, wherein said radiant energy is radio-frequency, microwave, laser light or ultrasound.

7. The method of claim 6, wherein said arcuate cutting devices additionally act as antennas emitting radio-frequency radiation, with adjacent arcuate cutting devices alternately being active or ground, so as to provide a circumferential radio-frequency energy field.

8. The method of claim 2, further comprising radiating energy from said at least one arcuate cutting device, wherein said at least one arcuate cutting device is hollow and said radiated energy accomplishes at least one of cutting said channel, curing said encapsulating composition and incapacitating cancer cells in said tissue.

9. The method of claim 8, wherein said radiating energy is radio-frequency, microwave, laser light or ultrasound.

10. The method of claim 1, wherein said channel is provided by cutting tissue adjacent to said tissue with a hollow cutting device, and said encapsulating composition is discharged from said hollow cutting device.

11. The method of claim 10, wherein said encapsulating composition is discharged from said hollow cutting device during or after providing said channel.

12. The method of claim 1, wherein said capsule predominantly comprises ingredients of said encapsulating composition.

13. The method of claim 12, wherein said capsule further comprises native materials contributed by said organism in response to said operation.

14. The method of claim 1, wherein said encapsulating composition comprises collagen.

15. The method of claim 1, wherein said encapsulating composition comprises a synthetic film-forming agent.

16. The method of claim 1, wherein said encapsulating composition comprises a marking agent.

17. The method of claim 1, wherein said encapsulating composition comprises a radiation-enhancing agent.

18. The method of claim 1, further comprising evacuating said capsule of its contents.

19. The method of claim 18, wherein said capsule contents are liquified, vaporized or comminuted prior to said evacuating.

20. The method of claim 19, wherein said capsule contents are comminuted by at least one rotating blade, cord or wire.

21. The method of claim 18, wherein prior to said evacuating, said capsule contents are contacted with at least one of a desiccant, a cell bursting agent, a free-radical catalyst, a free-radical chemical reaction initiator, a halogenator, and an enzyme, to incapacitate cancer cells in said capsule and increase fluidity of said capsule contents.

22. The method of claim 18, wherein prior to said evacuating, said capsule contents are contacted with at least one of ultrasound, laser, microwave and radio-frequency energy, to incapacitate cancer cells in said capsule and increase fluidity of said capsule contents.

23. The method of claim 22, wherein ultrasound energy having a wavelength of about 20 to about 40 kilohertz is applied to liquify said capsule contents.

24. The method of claim 1, further comprising impeding fluid communication between said tissue and other tissue in said organism prior to providing said channel.

25. The method of claim 24, wherein said impeding is facilitated by contacting peritumoral tissue with at least one member selected from the group consisting of blood isolated from said patient, a vasoconstrictor, ferric lactate, a sclerosing solution, ethyl alcohol, minocycline, a tissue factor, fibrinogen, fibrin, collagen, gelatin and distilled water.

26. The method of claim 24, wherein said impeding is facilitated by injecting a solution comprising epinephrine into said peritumoral tissue.

27. The method of claim 24, wherein said impeding is facilitated by injecting a solution comprising hemolyzed blood into said peritumoral tissue.

28. The method of claim 18, further comprising sterilizing an interior surface of said capsule after said evacuating.

29. The method of claim 28, wherein said interior surface is sterilized by applying to said surface at least one of a chemical sterilant, a biological sterilant, heat, ultrasound and electromagnetic radiation.

30. The method of claim 18, further comprising removing said capsule after said evacuating.

31. The method of claim 30, further comprising implanting in or adjacent a void created by removal of said capsule and evacuation of said capsule's contents, at least one of a sustained-release chemotherapeutic agent, a sustained-release

sterilization agent, a sustained-release biological response modifying agent, a free-radical catalyst, a free-radical reaction initiating agent, and a locally-persisting radiation-enhancing agent.

32. The method of claim 18, wherein said capsule is not removed from said organism, and said method further comprises including in said encapsulating composition or implanting within or adjacent said capsule, at least one of a sustained-release chemotherapeutic agent, a sustained-release sterilization agent, a sustained-release biological response modifying agent, a free-radical catalyst, a free-radical reaction initiating agent, and a locally-persisting radiation-enhancing agent.

33. An apparatus for performing the method of claim 1, said apparatus comprising a multipurpose hollow needle-blade antenna energy deposition array which cuts said channel, delivers said encapsulating composition into said channel, and radiates energy within the capsule.

34. An apparatus for performing the method of claim 1, said apparatus comprising a wand provided with at least one pressurizable fluid inflow channel and at least one negative pressurizable fluid outflow channel.

35. A method for conducting an operation on a living organism, said method comprising:

providing a channel around a tissue of said organism;

infusing into said channel an encapsulating composition to encapsulate said tissue in a capsule; and

conducting said operation on said tissue within said capsule,

wherein said capsule defines an operational field to which said operation is confined.

36. The method of claim 35, wherein said treating comprises dispensing into said capsule a pharmaceutically active composition, and said capsule prevents said pharmaceutically active composition from contacting other tissue outside said capsule.

37. The method of claim 35, wherein said treating comprises dispensing energy into said capsule, and said capsule focuses said energy within said capsule.

38. The method of claim 35, further comprising evacuating said treated tissue from said capsule.

39. An improved method for administering radiation therapy to tissue in a living organism, comprising administering to said tissue or near said tissue a locally persisting formulation of at least one agent selected from the group consisting of a catalytic metal, iodine, a transition metal, a noble metal or a high atomic number metal.

40. The method of claim 39, wherein said agent has a tissue half-life in excess of 3 hours.

41. The method of claim 40, wherein said tissue half-life is in excess of 24 hours.

42. The method of claim 39, wherein said agent is administered in an amount effective to: (a) increase free-radical formation, (b) propagate free-radical reactions, (c) prevent free-radical extinction, and/or (d) catalyze cell damaging chemical reactions which are initiated by ionizing radiation.

43. The method of claim 42, wherein said formulation comprises a colloidal or particulate form of an iron, copper or vitamin C compound.

44. The method of claim 43, wherein said formulation is directly injected in a prostate gland containing cancerous tissue.

45. The method of claim 42, wherein said at least one agent is a compound of iron, and said method further comprises systemically administering to said living organism an iron chelating agent.

46. The method of claim 1, further comprising administering to said tissue or near said tissue a locally persisting formulation of an iron compound, and systemically administering to said living organism an iron chelating agent.

47. The method of claim 1, wherein said encapsulating composition comprises a photoinitiator and a photopolymerizable hydrogel, and said method further comprises photopolymerizing said hydrogel in situ to provide said capsule.

48. The method of claim 47, wherein said hydrogel comprises polyethylene glycol and said photoinitiator is 2,2-dimethoxy-2-phenyl acetophenone.

49. The method of claim 47, wherein said hydrogel comprises a poly(propylene fumarate-co-ethylene glycol).

50. The method of claim 1, further comprising impeding fluid communication between said tissue and other tissue in said organism prior to providing said channel by injecting around said tissue a plasticizing composition comprising polyethylene glycol and a photo-initiating agent, wherein said plasticizing composition is effective to raise extracellular fluid viscosity and induce transient tissue solidification.

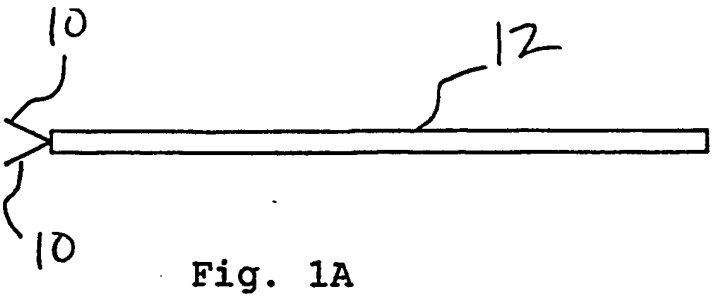

Fig. 1A

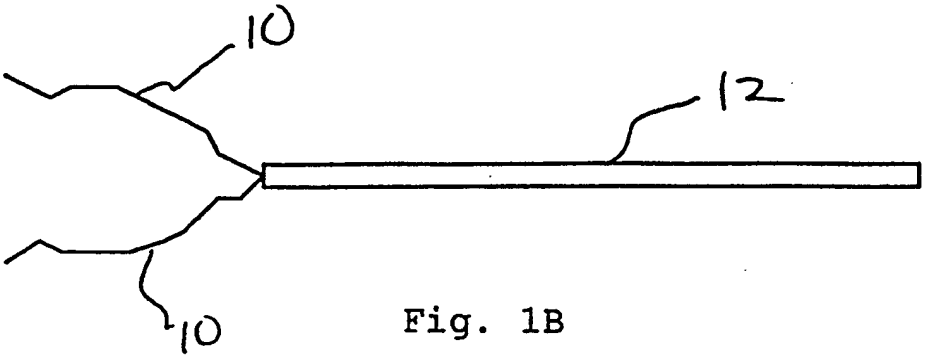

Fig. 1B

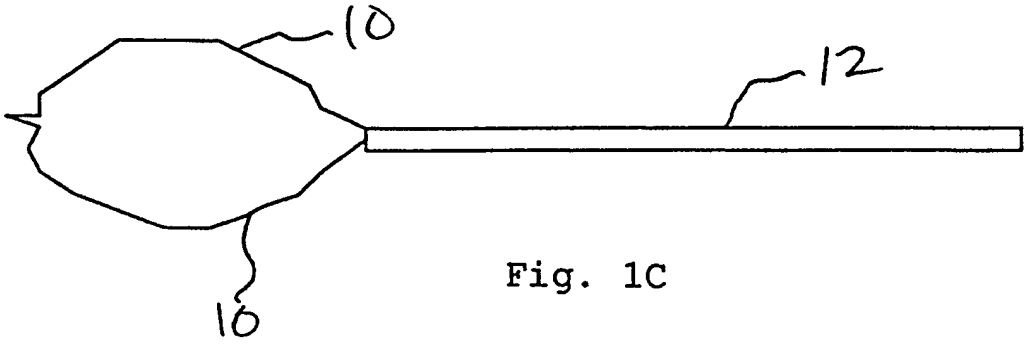

Fig. 1C

Fig. 2

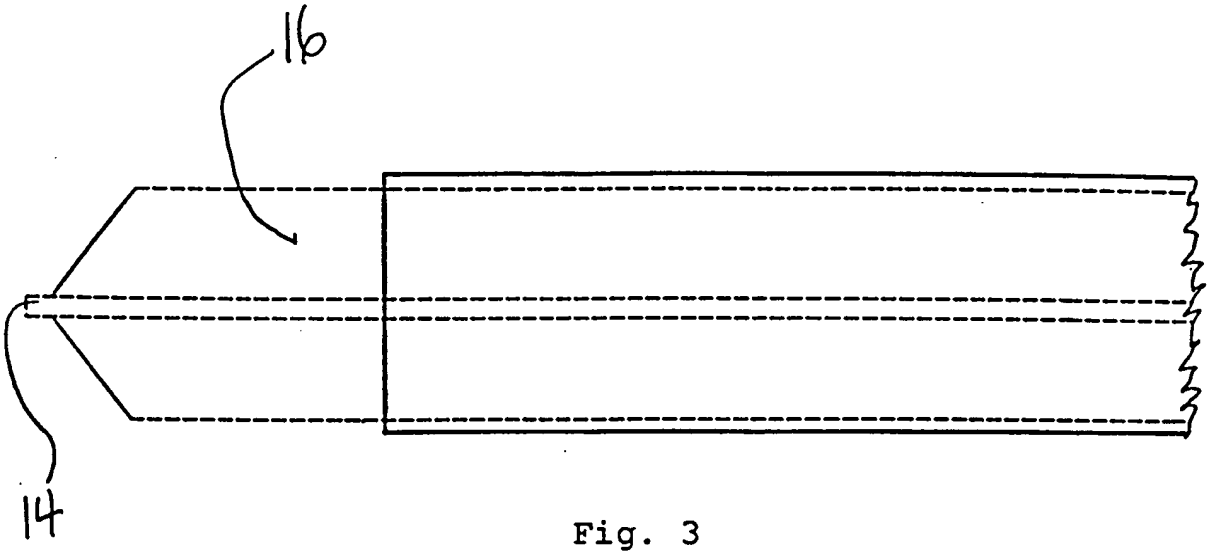

Fig. 3

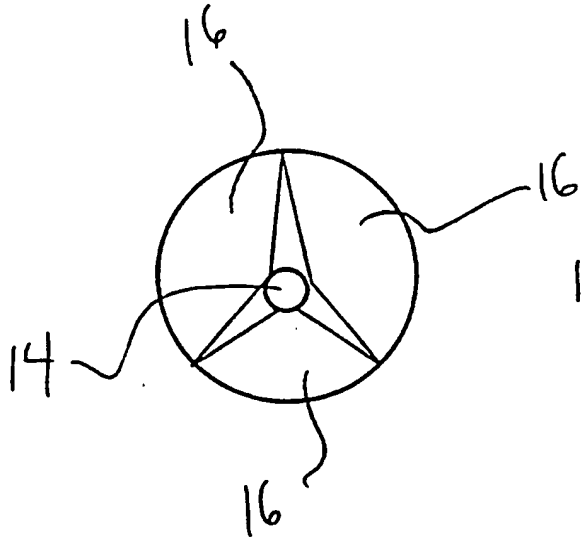

Fig. 4

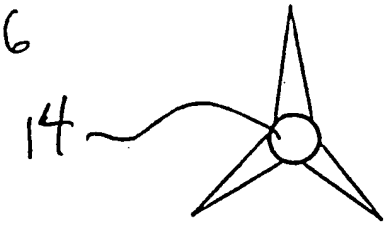

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/23595

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00
US CL :128/898

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 424/646-648; 514/23, 502, 549, 560; 604/21, 22; 606/27-29, 31, 41, 45-50; 607/96, 98-102, 115, 116, 120, 154

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, EAST

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 5,246,726 A (HORROBIN et al.) 21 September 1993, entire document.	1-50
A	US 5,458,597 A (EDWARDS et al.) 17 October 1995, entire document.	1-50
A	US 5,472,441 A (EDWARDS et al.) 05 December 1995, entire document.	1-50

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search
06 DECEMBER 1999

Date of mailing of the international search report
04 FEB 2000

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231
Facsimile No. (703) 305-3230

Authorized officer
KELLY O'HARA

Telephone No. (703) 308-0780